

Linking Dorsal Raphe Volume to Depression and Anxiety in Aging and Early Alzheimer's

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BACKGROUND

- **Depression and anxiety** are common in aging and early Alzheimer's disease (AD) and have been closely linked to serotonergic dysfunction.
- Postmortem studies indicate that the **dorsal raphe nucleus** (DR), a key serotonergic hub, is affected early in AD (**Braak 0**), but in vivo evidence of its relationship with affective symptoms is limited.
- We investigated whether DR volume is associated with depressive/anxiety symptoms across aging and early AD.

METHODS

96 participants (24 healthy controls, 41 mild cognitive impairment [MCI] due to AD, 31 AD dementia) underwent biomarker confirmation (CSF biomarkers for AD cases, plasma pTau217 negative in controls), neuropsychiatric assessment (Geriatric Depression Scale [GDS] and Hamilton Anxiety Scale [HAM-A]), and **3T MRI** including T1 and turbo spin echo sequences.

DR volume was quantified, with medial raphe and hypothalamus volumes, and locus coeruleus integrity, used as anatomical controls. **Correlations** between MRI measures and GDS/HAM-A scores were performed. **Linear regression models** examined the relationship between DR volume and GDS/HAM-A, adjusting for age, diagnosis, and interaction with SSRI (selective serotonin reuptake inhibitor) treatment.

RESULTS

Higher GDS and HAM-A scores were observed in early AD compared to controls. **DR volume negatively correlated with GDS** ($r = -0.31$, $p = 0.0026$) and **HAM-A** ($r = -0.25$, $p = 0.015$). No significant associations were observed for anatomical control regions (medial raphe, hypothalamus or LC), **Figure 1**. **Regression analyses confirmed these associations independent of age, sex, diagnostic group and ISRS treatment** (GDS: $\beta = -0.22$, $p = 0.008$; HAM-A: $\beta = -0.216$, $p = 0.032$). Similar results were observed when diagnostic status was modelled according to AD stage (healthy controls, MCI and dementia), with DR volume remaining significantly associated with GDS scores ($\beta = -0.22$, $p = 0.013$), but not with HAMA scores (**Figure 2**).

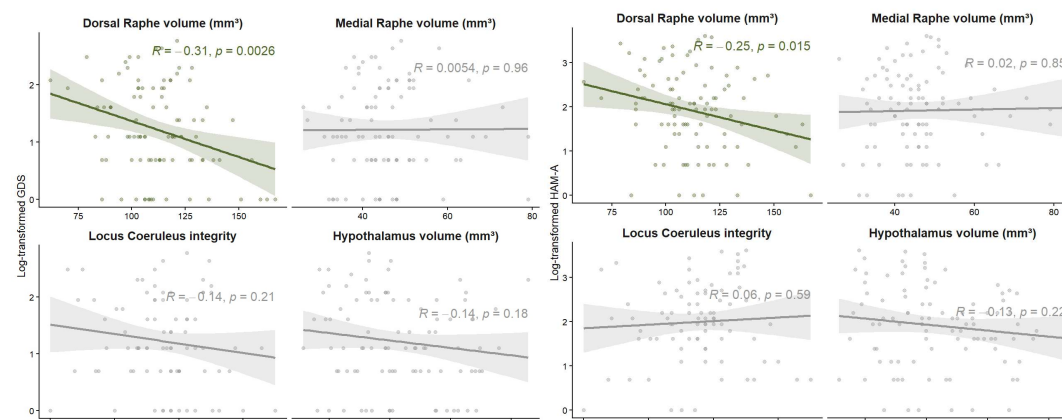


Figure 1. Correlations of affective symptoms with DR and control regions.

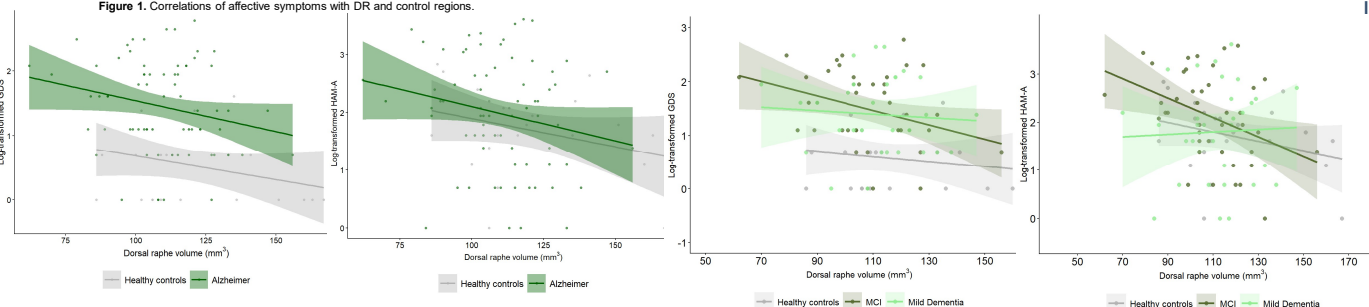


Figure 2. Regression models linking DR volume to affective symptoms.

CONCLUSIONS

- **Lower DR volume** is associated with **higher depressive and anxiety symptoms** across aging and early AD, consistent with its serotonergic function.
- The observed interaction with SSRI highlights that medication status can influence these associations.
- These findings provide in vivo evidence linking DR structure to affective symptoms, supporting the relevance of **serotonergic circuits** as potential targets for intervention.

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